REMARKS

The foregoing amendments to the claims are of a formal nature and do not add new matter. Claims 42-44 have been amended to include a definition of the ECD. Support for this amendment can be found in the Specification as filed, for example Figure 2, and page 16, lines 3-13. Claim 50 has been amended to depend from Claim 42. Claim 51 has been amended to replace "epitope tag" with "tag polypeptide" to clarify the claim. Support for this amendment can be found, for example, on page 23 of the Specification. Claims 42-51 remain present for further examination. The changes made to the specification and claims by the current amendment are shown herein with deletions designated with a strikethrough and additions underlined.

Correction of Inventorship under 37 CFR §1.48(b)

The Examiner has refused to accept the request to delete inventors because it was not in the form of a petition. Applicants respectfully disagree that a petition is required.

37 C.F.R. §1.48(b) states that

> If the correct inventors are named in a nonprovisional application, and the prosecution of the nonprovisional application results in the amendment or cancellation of claims so that fewer than all of the currently named inventors are the actual inventors of the invention being claimed in the nonprovisional application, an amendment must be filed requesting deletion of the name or names of the person or persons who are not inventors of the invention being claimed. Amendment of the inventorship requires:
>
> (1) A request, signed by a party set forth in §1.33(b), to correct the inventorship that identifies the named inventor or inventors being deleted and acknowledges that the inventor's invention is no longer being claimed in the nonprovisional application; and
>
> (2) The processing fee set forth in §1.17(i) (emphasis added).

Applicant properly submitted a request that Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen and Colin K. Watanabe be deleted as inventors, and included a statement that "these inventors' inventions are no longer being claimed in the present application" as a result of prosecution. The fee as set forth in § 1.17(i) was duly submitted. Accordingly, Applicants respectfully submit that they have complied with 37 C.F.R. §1.48(b) and request that the four named inventors be deleted from the application.

Objection to the Specification

The Specification was previously amended to clarify priority information. The Examiner objected to the amendments filed 1/8/02 and 7/16/02 as introducing new matter. While Applicants disagree with the Examiner's position, in order to expedite prosecution, Applicants had previously cancelled this added information. The paragraph containing the priority information as amended in Applicants previous reply is set forth on page 2 of this paper. This paragraph does not contain the information added by amendment on 1/8/02 and 8/16/02. This paragraph in its current form claims priority only to those applications listed in the application as originally filed, and the changes do affect the priority claimed in the present application.

Rejection under 35 U.S.C. § 101

The Examiner maintains his rejection of Claims 42-51 as allegedly not supported by a substantial asserted utility or a well established utility. The Examiner asserts that the gene expression data disclosed in Example 18 of the present application and the table therein does not satisfy the utility requirements of 35 U.S.C.§101 for the polypeptide.

In support of his position, the Examiner states that he previously provided examples of references that show that gene expression data is unpredictable with regard to protein over-expression and cited the following paragraph from Gene VI, Benjamin Lewin, 1997, Chapter 29 – Regulation of Transcription, 1st page:

> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription.

The Examiner asserts that this citation, as well as the additional references cited, are examples that the art is unpredictable with regard to protein over-expression. Applicants respectfully disagree, and offer the following arguments in support of the claimed utility.

Utility Guidelines

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." A utility is "specific" when it is particular to the subject matter claimed. For example, it is

generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantially utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a 'substantial' utility." (M.P.E.P. 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P., 2107 II(B)(1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record ... that is probative of the Applicant's assertions." (M.P.E.P. 2107 II(B)(1)(ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the

Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants rely on the gene amplification data for patentable utility for this case, which was first disclosed in the PCT/US00/23328, filed August 24, 2000. Applicants have properly claimed and are entitled to the priority of the effective filing date of **August 24, 2000**. As will be apparent from the discussions below and the supporting evidence, Applicants submit that the results of PCR provide specific and substantial asserted utility for the claimed polypeptides in this invention. Since this utility was disclosed in PCT/US00/23328, the claims pending are fully entitled to the priority of August 24, 2000.

Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. The gene expression data in the specification on page 93, Example 18 shows that the mRNA for PRO180 was more highly expressed in tumor versus normal tissue. Gene expression was identified using standard quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type rendered the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor, as well as therapeutically, as a target for the treatment of a tumor in a subject possessing such a tumor.

Applicants further submit that it is generally well-understood in the art that in the majority of cases, gene expression correlates with levels of protein expression. In support of Applicants' position, Applicants have previously submitted the declaration of J. Christopher Grimaldi (filed with the amendment dated January 28, 2004). The Examiner states that gene expression and protein expression are questionably correlated, and cites the following for support:

> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production

> <u>of protein</u>, ***it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription*** (emphasis added).

The sentence states that "it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription". This in fact supports Applicants' assertion that in the majority of cases, when the mRNA is over-expressed, the gene product is also over-expressed.

In reality, scientists regularly rely on the results of gene expression and even gene amplification results to point the way to differential protein expression in disease and, in this case, cancer. Submitted herewith is the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Additional references support this position. For example, Orntoft et al. (submitted herewith) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft et al. showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman et al. (submitted herewith) showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels" (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack et al. (submitted herewith) who studied a series of primary human breast tumors and found that "...62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels" (see column 1, abstract). Thus, these articles collectively teach that in general, gene amplification correspondingly increases mRNA expression.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of cases, the combined teachings in the art, exemplified by Orntoft et al., Hyman et al. and Pollack et al. and the Grimaldi and Polakis declarations, overwhelmingly teach that gene amplification influences gene expression and that gene expression influences protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the gene expression data for the PRO180 gene, that the PRO180 protein is concomitantly over-expressed. Thus, Applicants submit that the PRO180 proteins and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

Claimed proteins would have diagnostic utility even if the protein were not over-expressed

Even assuming *arguendo* that, there is no correlation between gene expression and increased protein expression for PRO180, which Applicants submit is not true, a polypeptide

encoded by a gene that is over-expressed in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit herewith the Declaration of Avi Ashkenazi, Ph.D., an expert in the field of cancer biology. Dr. Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants submit that simultaneous testing of gene expression (or gene amplification) and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Even if not over-expressed, a polypeptide encoded by a gene that is over-expressed in cancer would still have utility. Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO180

polypeptide. Based on the evidence and arguments presented herein, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Applicants have provided several expert opinions supporting the utility of the present invention. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made by Mr. Grimaldi, Dr. Polakis and Dr. Ashkenazi, and must treat as true the statements made by these experts. Applicant reminds the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001).

Applicants believe that they have met their burden of establishing a specific and substantial credible utility for the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §101 be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner also maintained his rejection of Claims 42-51 under 35 U.S.C. §112, first paragraph as not having a specific utility. However, for the reasons outlined above in response to the rejection under 35 U.S.C. §101, Applicants believe they have established the utility of the claimed invention and therefore respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner maintained his rejection of Claims 42-51 because the Examiner believes that the ECD is described not by what it is, but by what it is not. The claims have been amended to recite the specific ECD regions. Thus, Applicants submit that the claims as amended are definite, and request that the rejection be withdrawn.

The Examiner rejected Claim 51 as being indefinite for reciting an "epitope tag," because the exact meaning of the language is not clear. The term "epitope tag" has been deleted from the claim, and replaced with "tag polypeptide." The definition of a tag polypeptide is well-known by those of skill in the art, and is further set out in the Specification as filed on page 23, lines 24-30. Applicants submit that the claim as amended is definite and requests that the rejection be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph, Written description

The Examiner maintains the rejection of Claims 42-43 and 50-51 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the Examiner, only SEQ ID NO:1 is amplified in tumors which encodes SEQ ID NO:2, and there is no polypeptide that is overexpressed in rectal tumors. The specification does not describe any other nucleic acid that encodes any polypeptide that is 95-99% identical to SEQ ID NO:2, which is encoded by a nucleic acid that is over-expressed in rectal tumors.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequate of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

In the arguments presented above, Applicants have established the utility of the claimed polypeptides, arguing that it is more likely than not that since SEQ ID NO:1 is amplified in rectal tumors, the polypeptide of SEQ ID NO:2 is over-expressed in rectal tumors. The Specification provides sufficient disclosure of other polypeptides that are 95% or 99% identical to SEQ ID NO:2.

The present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The instant invention, defined by the amended claims, concerns polypeptides having 95% or 99% sequence identity with the disclosed polypeptide sequences SEQ ID NO:2 and further, with the functional recitation: "wherein the nucleic acid encoding said polypeptide is amplified in rectal tumors." Based on the detailed description of the cloning and expression of variants of PRO180 in the specification, the description of the gene amplification assay and description of testing the ability of test variant polypeptides in the assay, the actual reduction to practice of sequences SEQ ID NO:2 and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the invention as claimed in the instant claims.

Hence, Applicants submit that this rejection should be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph, Enablement

The Examiner has rejected Claims 42-43, and 50-51 under 35 U.S.C. §112, first paragraph, as not being enabled. According to the Examiner, the specification does not describe how to make polypeptides that are 95-99% identical to SEQ ID NO:2 wherein the nucleic acid

over-expressed. In addition, the Examiner cites references that demonstrate protein over-expression does not correlate with mRNA over-expression.

As pointed out above, Applicants have established the utility of the claimed polypeptides, arguing that it is more likely than not that since SEQ ID NO:1 is amplified in rectal tumors, the polypeptide of SEQ ID NO:2 is over-expressed in rectal tumors. The Specification provides sufficient disclosure to enable one of skill in the art to make and use other polypeptides that are 95% or 99% identical to SEQ ID NO:2.

Based on utility for the PRO180 gene and the nucleic acids encoding the polypeptides in the diagnosis of rectal cancer, as discussed above, Applicants submit that the skilled artisan would not require undue experimentation to make and use the claimed invention. Accordingly, Applicants request that this rejection be withdrawn.

Rejections under 35 U.S.C. §102(b) – Feng et al.

The Examiner maintained the rejection of Claims 42-45, 47, and 50-51 as anticipated under 35 U.S.C. § 102(b) by Feng et al (WO 99/24836, published May 1999). Because of the allegations of the lack of utility for the claimed invention, the Examiner has accorded an effective priority date for this application of its instant filing date. Consequently, the Examiner has cited this reference as prior art against the instant claims and has alleged that the claims are unpatentable in view of this reference. Applicants respectfully traverse.

Applicants are entitled to priority to U.S. Provisional Application No. 60/096,012 filed on **August 10, 1998**. This application includes the disclosure of the full length sequence of SEQ ID NOS:1 and 2. As the August 10, 1998 date precedes the date of the Feng et al. reference (May 1999), Applicants have shown possession of the claimed invention prior to the Feng reference.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the

application claims priority back to a disclosure that predates the cited references. Applicants demonstrated, by means of the disclosure in their provisional application filed August 10, 1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID NO:2, as disclosed in the Feng et al. reference dated May 1999. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §102 be removed.

Rejection under 35 U.S.C. §102(b) – Baker et al.

The Examiner has maintained the rejection of Claims 42-51 as being anticipated by Baker et al. (WO 99/63088, published 12/99). The Examiner states that because the present application is entitled to priority only to its filing date due to a lack of utility, the 131 Declaration previously submitted cannot be used to antedate the Baker reference.

Applicants respectfully disagree. As argued above, the priority date for the claimed invention which provides a utility is, in fact, **August 24, 2000**. Applicants maintain their position that the results of PCR provide specific and substantial asserted utility for the claimed polypeptides in this invention. Since this utility was disclosed in PCT/US00/23328, the claims pending are fully entitled to the priority of August 24, 2000.

The Declaration under 37 CFR §1.131 which was previously submitted establishes that the presently claimed invention antedates the Baker et al. reference. The Declaration and the supporting evidence submitted therewith established conception of the invention prior to the 12/99 publication date of Baker et al., and diligent reduction to practice thereafter. Withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Conclusion

The present application is believed to be in condition for allowance, and action to that effect is respectfully requested. Should the Examiner have any further questions, please contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 7, 2004

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